PRINS BICYCLIZATION STRATEGY FOR THE STEREOSELECTIVE SYNTHESIS OF BRIDGED BENZOPYRAN, SUGAR ANNULATED FUROPYRAN HETEROCYCLES AND TOTAL SYNTHESIS OF (–) MALYNGOLIDE AND ITS C(5) EPIMER

A SYNOPSIS

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By

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The thesis entitled "**Prins Bicyclization Strategy For The Stereo selective Synthesis of Bridged Benzopyran, Sugar Annulated Furopyran Heterocycles and Total Synthesis of (—) Malyngolide and its C(5) Epimer**" has been divided into five chapters.

Chapter I: This chapter deals with the introduction and application over Prins reaction.

Chapter II: This chapter deals with the Tandem Prins cyclization For the stereoselective synthesis of bridged benzopyran derivatives **Chapter III**: This chapter deals with a novel Prins bicyclization strategy for the first stereoselective synthesis of sugar annulated furo-[3,2-*c*]pyran scaffolds.

Chapter IV: This chapter deals with facile synthesis of 9a*H*,15*H*[1] benzopyrano[3',2':3,4]pyrido[2,1-*a*]isoquinolines and oxazinoisoquino-lines *via* 1,4-dipolar cyclo-addition reactions in ionic liquid.

Chapter V: Total Synthesis of (—)-Malyngolide and its C(5)-Epimer.

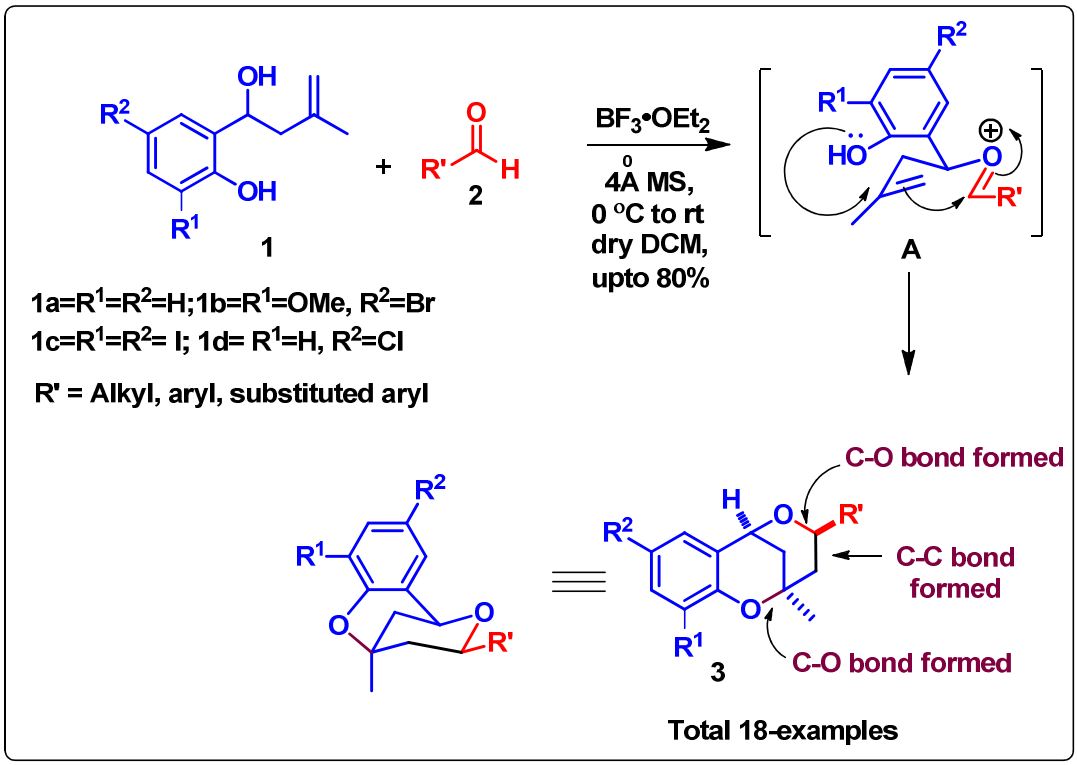
CHAPTER I: Introduction

This chapter focuses on the historical overview of Prins reaction, its recent development and its applications over synthesis of core motif of various natural products. This chapter also describes the importance of bicyclization approach for synthesizing new types of heterocycles in an efficient and efficacious way in the field of natural products synthesis.

CHAPTER II: Tandem Prins Cyclization For the Stereoselective Synthesis of Bridged Benzopyran Derivatives

Heterocycles are playing a very important role in the field of pharmaceutical industry which always drawn the attention of organic chemists for the generation of new drugs along with pharmaceuticals. Stereoselective construction of complex heterocycles has always been a continued challenge for an organic synthetic chemist. To construct these core motif, various approaches have been developed. Among them "Cascade/Domino reactions" constitute a fascinating branchin an organic chemistry. Recently Prins Cascade cyclization reaction has proven to play an immense role in the field of organic synthesis which revealed its efficacy in achieving molecular complexity and diversity. However, this cascade process has not been till explored for the synthesis of biologically relevant benzodioxocine derivatives by using a homoallylic alcohol tethered with a phenolic group.

We have developed a novel Prins cascade strategy for the stereo-selective synthesis of 3,4-dihydro-2*H*,6*H*-2,6-methanobenzo[*b*][1,5]dioxocine derivatives **3** up to 80% yield from 2-(1-hydroxy-3-methylbut-3-en-1-yl)phenol **1** with various class of aldehydes **2** catalysed by 10 mol% of $BF_3{\cdot}OEt_2$ in DCM. This is the first report on the stereoselective construction of bridged dioxabicyclic skeleton through a cascade of Prins bicyclization. It is an elegant strategy for the quick construction of tricyclic moiety in a single step (Scheme 1).



Scheme 1

Structural Conformation : The structure and stereochemistry of **3** was confirmed by both NMR and X-ray crystallographic studies.

NMR studies :

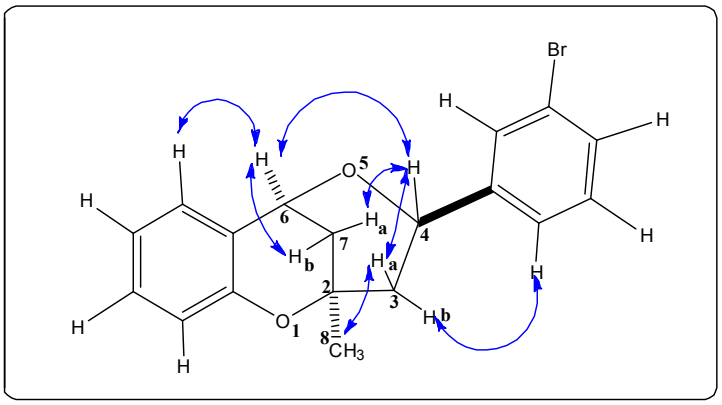


Fig. 1 Energy minimized diagram of bridged dioxabicyclic moiety

NMR studies of **3** including 1D (1H, 1H-1H Homo-nuclear Decoupling and 13C) and 2D (DQCOSY, NOESY, TOCSY, HSQC and HMBC) confirmed its structure and stereochemistry. The energy

minimized diagram of bromo derivative of bridged dioxabicyclic scaffold as shown in (Fig 1).

X-ray Crystallography Studies :

The stereochemistry and characterization of product **3** was further confirmed by X-ray crystallographic studies also. The ORTEP diagram of one of the chloro derived product **3** is shown in (Fig. 2).

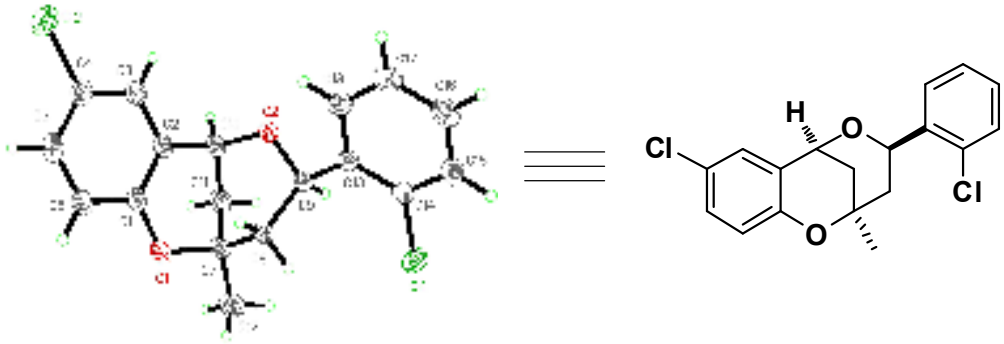


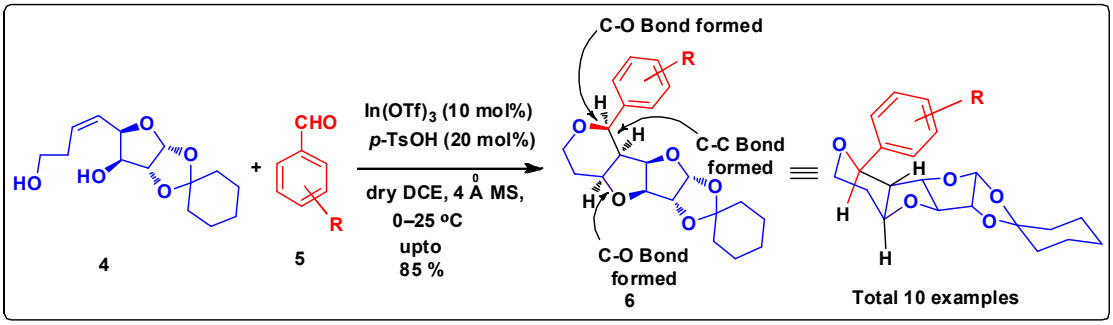
Fig. 2 ORTEP diagram of bridged benzopyran

In conclusion, we have developed a novel cascade strategy for the synthesis of bridged tricyclic benzopyran derivatives. The reaction is highly diastereoselective and provides the desired products in good yields in short reaction time.

CHAPTER III: A Novel Prins Bicyclization Strategy For The First Stereoselective Synthesis of Sugar Annulated Furo[3,2-*c*]pyran Scaffolds

A novel method for the synthesis of sugar-annulated furo[3,2-*c*]pyran derivatives **6** through Prins bicyclization from sugar-based homoallylic diols and aldehydes. In a model reaction, we first attempted the cross-coupling of sugar homoallylic diol **4** with benzaldehyde derivative **5** in the presence of **4** Å MS using 10 mol%

$In(OTf)_3$ and 20 mol% *p*-TSOH in dry DCE.

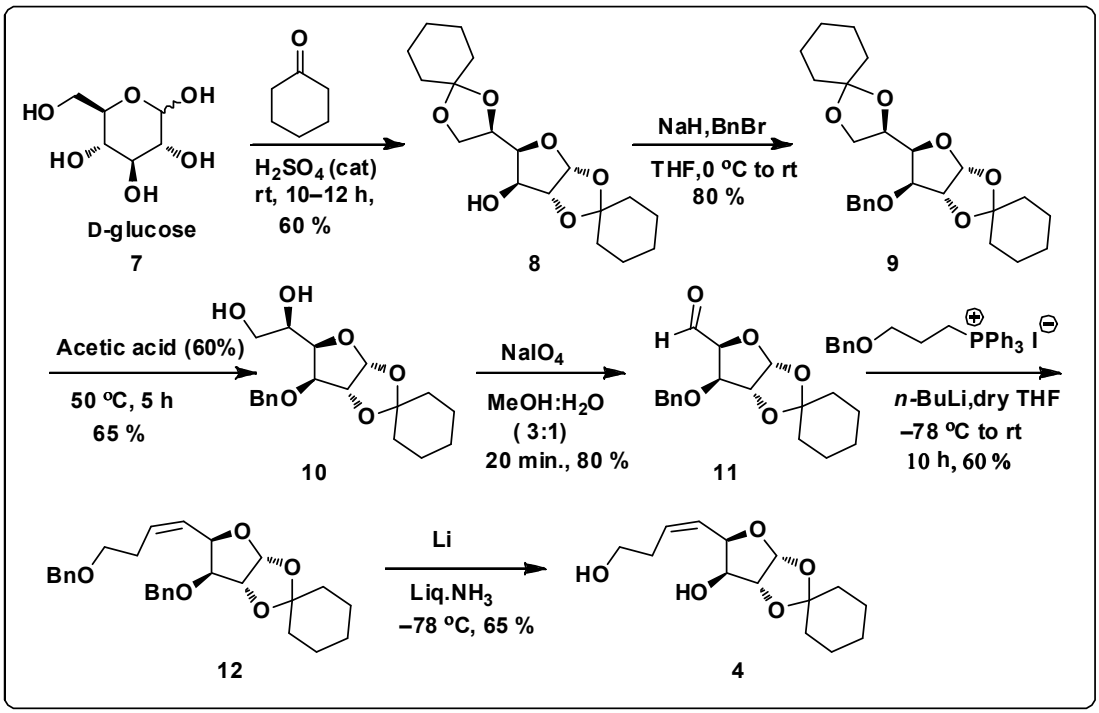


Scheme 2

Interestingly, the reaction proceeded smoothly at room temperature and the corresponding product **6** was obtained up to 80% yield with *cis* selectivity (Scheme 2).

Preparation of Starting material Homoallyl diol 4 in (Scheme 3)

Glucofuranose dicyclohexonide **8** was first prepared from D-glucose **7** by treating with cyclohexanone and catalytic amount of sulphuric acid. The free hydroxyl group of **8** was then protected as its benzyl ether using benzyl bromide in presence of sodium hydride at 0 °C in THF to give compound **9**, which when subjected to chemo-selective deprotection of primary hexonide, led to the product diol **10** in 65% yield. The oxidative cleavage of diol **10** with sodium periodate afforded the corresponding aldehyde **11**, which on Wittig olefination with Wittig salt derived from ((3-iodopropoxy)methyl)benzene under kinetic controlled condition led to diastereoselective *Z*-olefin product **12** in 60% yield. Finally, deprotection of benzyl ethers of **12** under Li metal and liq. NH_3 condition gave homoallyl diol **4** as starting material in 65% yield.



Scheme 3

Structural Conformation :

The structure and stereochemistry of **6** was confirmed by both NMR and X-ray crystallographic studies.

NMR studies : NMR studies of **6** including 1D and 2D (DQCOSY, NOESY) confirmed the fusion of the newly formed five membered ring with the six membered pyran, fully justifying its fused structure. The energy minimized diagram structure of sugar-annulated furo[3,2-*c*] pyran derivative is shown in (Fig. 3).

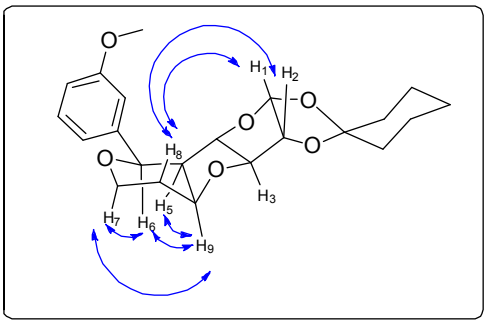


Fig. 3 Energy minimized diagram

X-ray Crystallography Studies :

The stereochemistry and characterization of product **6** was further confirmed by X-ray crystallographic studies also. The ORTEP diagram of one of the bromo derived product **6** is shown in (Fig. 4).

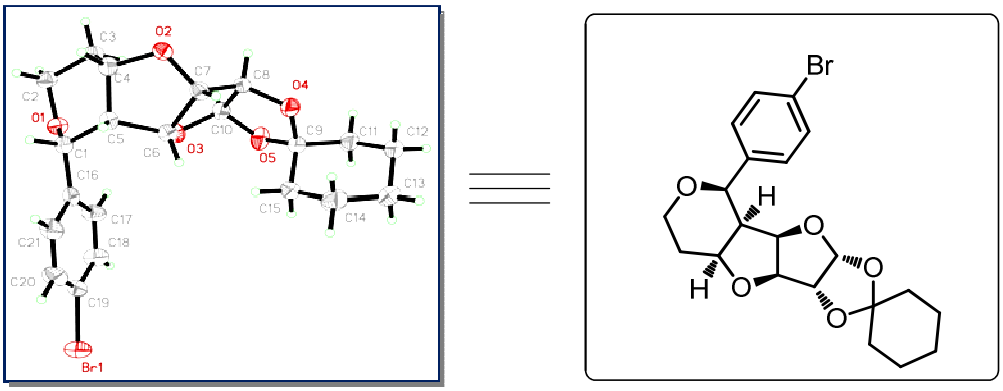


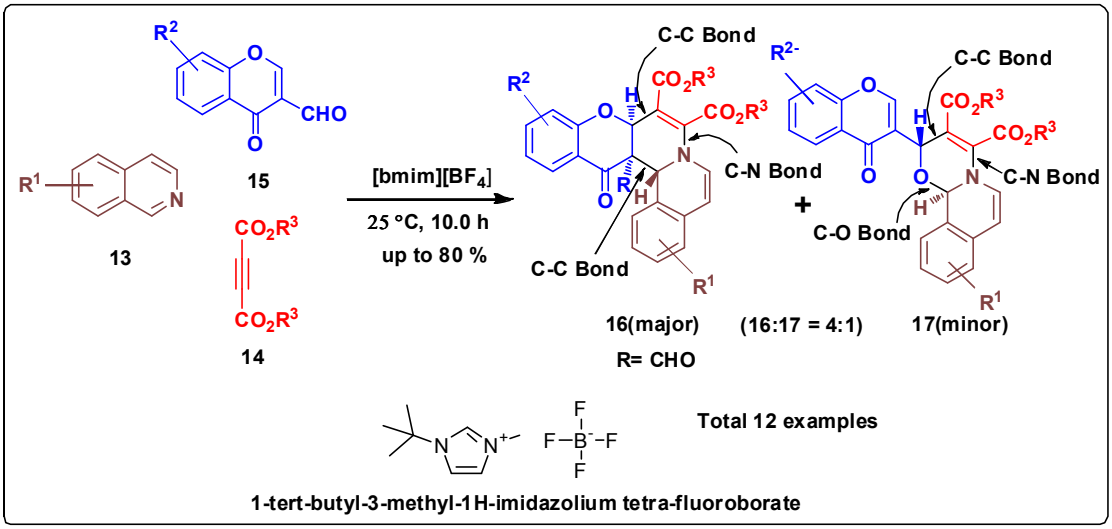
Fig. 4 ORTEP diagram of sugar-annulated furo[3,2-*c*]pyran **6**

In summary, we have demonstrated a novel approach for the synthesis of sugar-annulated furopyran derivatives through Prins bicyclization using a combination of $In(OTf)_3$ and *p*-TSOH. This method provides a direct access to the stereoselective synthesis of a wide range of sugar-fused furopyrans in a single-step process.

CHAPTER IV: Facile Synthesis of 9a*H*,15*H*[1]Benzopyrano[3',2':3,4]pyrido[2,1-*a*]isoquinolines and Oxazino-isoquinolines *via* 1,4-Dipolar Cyclo-addition Reactions in Ionic Liquid

A three component coupling reaction of isoquinoline or its derivatives **13**, dialkylacetylenedicarboxylate **14** and various 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde or chromone aldehyde **15** in [bmim][BF_4](1-tert-butyl-3-methyl-1*H*-imidazolium tetrafluoroborate ionic liquid media gave highly efficient synthesis of 9a*H*,15*H*-[1]benzopyrano[3',2':3,4]pyrido[2,1-*a*]isoquinoline **16** and its derivatives as

major product and Oxazino-isoquinolines **17** and its derivatives as minor product at room temperature.



Scheme 4

This coupling reaction gave a mixture of product **16**/**17** in a 4:1 ratio up to 80% yield (Scheme 4).

Structural Conformation :

X-ray crystallography studies :

The structure and relative configuration of **16** and **17** were confirmed by X-ray crystallographic studies (Fig. 5 and 6). The configuration of product **16** crystallized as hemiacetal form. The structure of the hemi- acetal derivative of **16a** was also confirmed by the ^{1}H-NMR spectrum ($CDCl_3$): The aldehyde H-atom of **16a** at δ (H) 9.98 (s, 1 H) was absent, and three new peaks at (δ) (H) 5.17 (d, J = 12.8 Hz, 1 H), 4.34 (d, J = 12.8 Hz, 1 H), and 3.31 (s, 3 H) were observed, which indicated the complete conversion of the aldehyde function to its hemiacetal derivative.

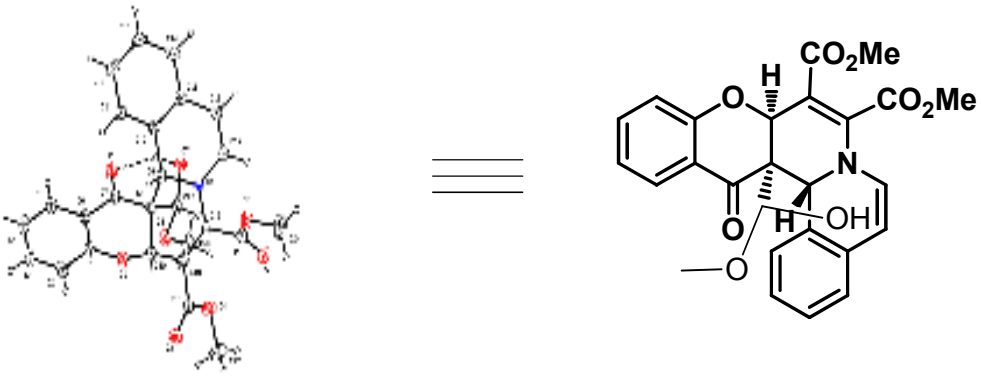


Fig. 5 ORTEP diagram of hemiacetal of compound **16**

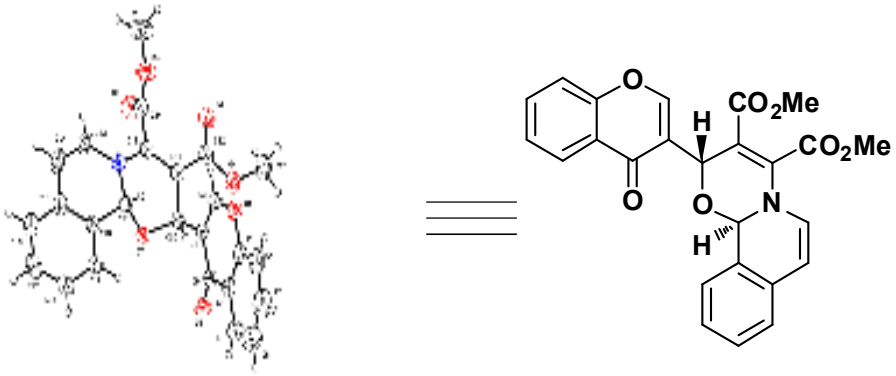


Fig. 6 ORTEP diagram of compound **17**

The crystal of hemiacetal of **16** belongs to the triclinic crystal system and the crystal of **17a** belongs to the orthorhombic crystal system.

In summary, we demonstrated the novel use of an ionic liquid as a convenient and recyclable reaction medium for the one-pot cyclo-addition of 4-oxo-4*H*-1-benzopyran-3-carbox-aldehydes with zwitter ionic adducts of isoquinolines and dimethyl or diethyl acetylene dicarboxylate to produce 9a*H*,15*H*[1]benzopyrano[3',2':3,4]pyrido [2,1-*a*]isoquinoline derivatives as major products along with oxazino-isoquinolines as minor products in good yields.

CHAPTER V: Total Synthesis of (—)-Malyngolide and its C(5)-Epimer

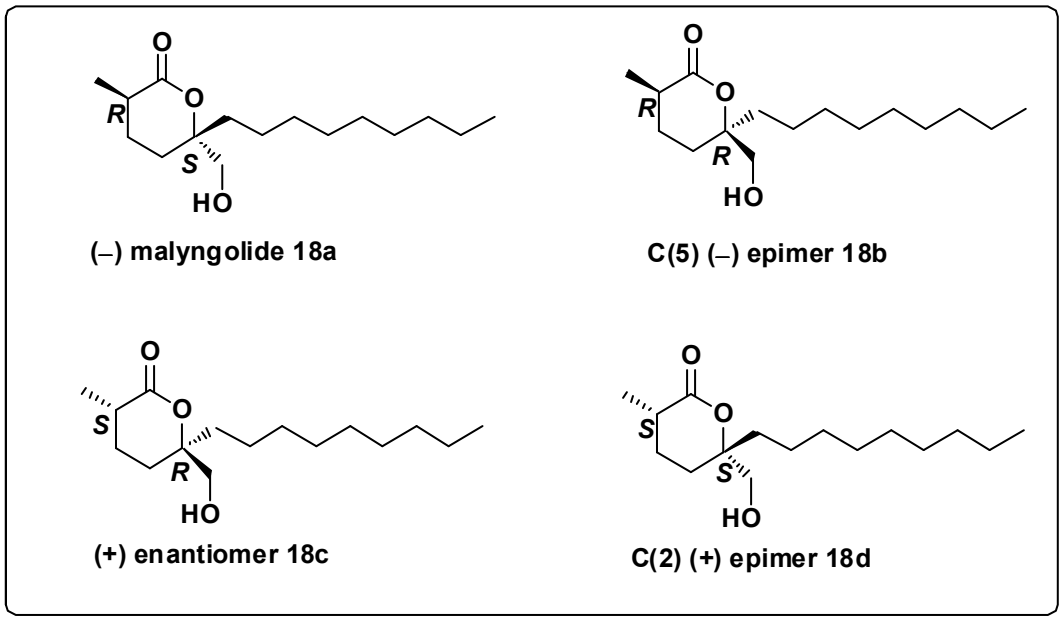
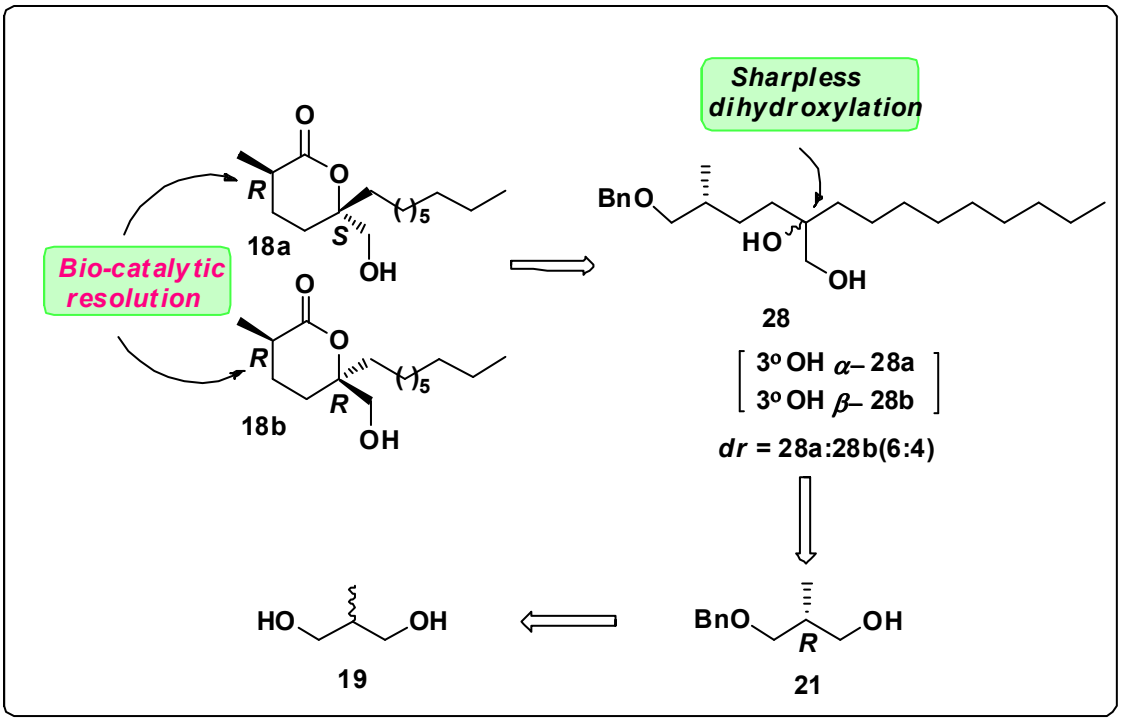


Fig. 7 Malyngolide and other stereoisomers

The six-membered *δ*-lactone containing natural products, for example (—)-malyngolides (**18a**) and its other stereoisomers **18**(**b-d**) (Fig. 7) were isolated as marine metabolites from the lipid extract of a blue-green algae, marine cyanobacterium *Lyngbya majuscula,* which was collected from the coast of Hawaii. Marine cyanobacteria are considered as a rich source of secondary metabolites, which are evaluated as potent anticancer agents.

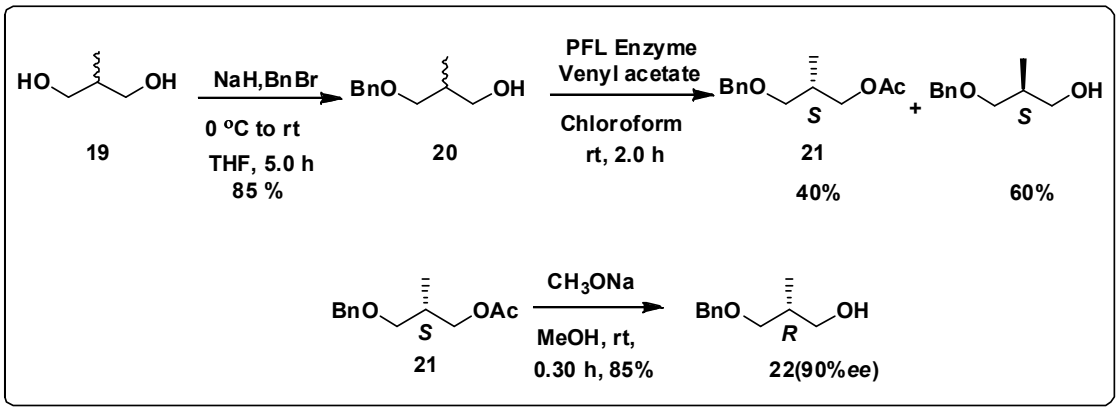
The cytotoxic studies of these marine metabolites against tumor cell lines are under clinical trials. In addition, some of them have been used as templates for the development of new anticancer drugs. Furthermore, many chemically diverse *δ*-lactones containing compounds are known to exhibit diverse biological activities such as

cytoxicity, anti-inflammatory and antibacterial behavior. Among them, (—)-malyngolide **18a** showed potential antibiotic activity against *Staphylococcus*, *Pseudomonas* and *Mycobacterium smegmatis*, but no activity against *E. coli* and *P. aeruginosa.* (—)-Malyngolide **18a** has drawn our interest towards its synthesis, because of its superior biological activity as compared to its other stereoisomers (Fig. 7).



Scheme 5

In our retrosynthetic analysis, we proposed that the target molecule was synthesized from the dihydroxylated compound **28** as a mixture of diastereomers **28a**/**28b** (6:4), which itself was synthesized from the chiral alcohol **21**, This chiral alcohol **21** was obtained from an enzymatic kinetic resolution process of racemic-2-methyl-propane-1,3 diol **19** (Scheme 5).

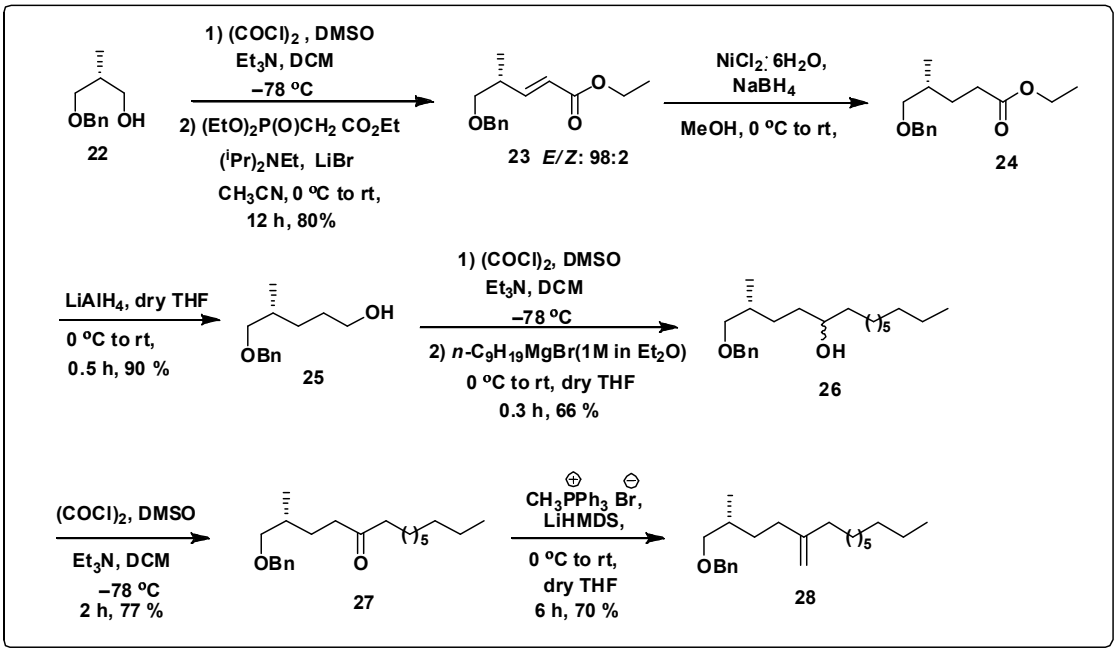


Scheme 6

Our synthesis began from commercially available racemic-2-methyl-propane 1,3, diol **19** which on treatment with benzyl bromide in presence of sodium hydride, resulting into mono protected racemic 3-(benzyloxy)-2-methyl-propane-1-ol compound **20** (Scheme 6). Then irreversible trans esterification of racemic 3-(benzyloxy)-2-methyl-propane-1-ol **20** with vinyl acetate catalyzed by *Pseudomonas fluorescens*lipase (PFL) enzyme in chloroform afforded enantio-merically pure chiral synthons *i.e.* acetyl protected compound **21** in 40% and unreacted alcohol in 60% yield (Scheme 6).

This resoluted compound **21** under treatment with sodium methoxide gave acetyl free pure alcohol compound **22** in 85% yield. This alcohol **22** with absolute stereochemistry *(R)* of methyl stereo-centre which is one of the imperative criteria for the antibiotic activity of malyngolide **18a**, was successfully achieved with nearly 90% *ee* and its configuration was assigned on the basis of ^{1}H-NMR analysis of its MTPA ester reported by P. Grisenti *et al.* In NMR studies, the MTPA ester from compound (*R*)-MTPA ester showed two doublets centred at δ 0.94 and 0.96 ppm in (95:5) ratio (Scheme 6).

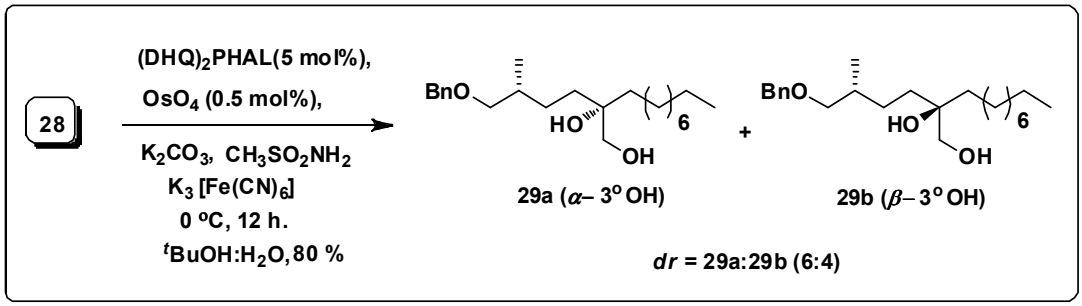
Oxidation of optically pure alcohol **22** under Swern conditions gave intermediate aldehyde which was further subjected to two carbon extension under Horner–Wadsworth Emmons protocol with triethyl phosphono acetate afforded the *α,β*-unsaturated ester **23** in 80% yield with 98/2 (*E/Z)* ratio (Scheme 7). Reduction of the C=C bond in compound **23** using NiB_4 (generated *in situ* from $NiCl_2{\cdot}6H_2O$ and $NaBH_4$ in MeOH) afforded the saturated ester **24** in 96% yield. Reduction of the saturated ester **4** with $LiAlH_4$ gave the mono-benzyl alcohol **25** with 90% yield.



Scheme 7

Oxidation of the resulted primary alcohol **25** under Swern conditions afforded an aldehyde, which upon treatment with *n*-nonyl magnesium bromide (2.0 equiv,1M in Et_2O) gave secondary alcohol product **26** as a mixture of diastereoisomers in a combined yield of 66%. Again subsequent oxidation of compound **26** under Swern protocol afforded ketone **27** in 77% yield. Wittig olefination of **27** with

methyl triphenyphosphonium bromide using LiHMDS furnished terminal olefin **28** in 70% yield (Scheme 7).



Scheme 8

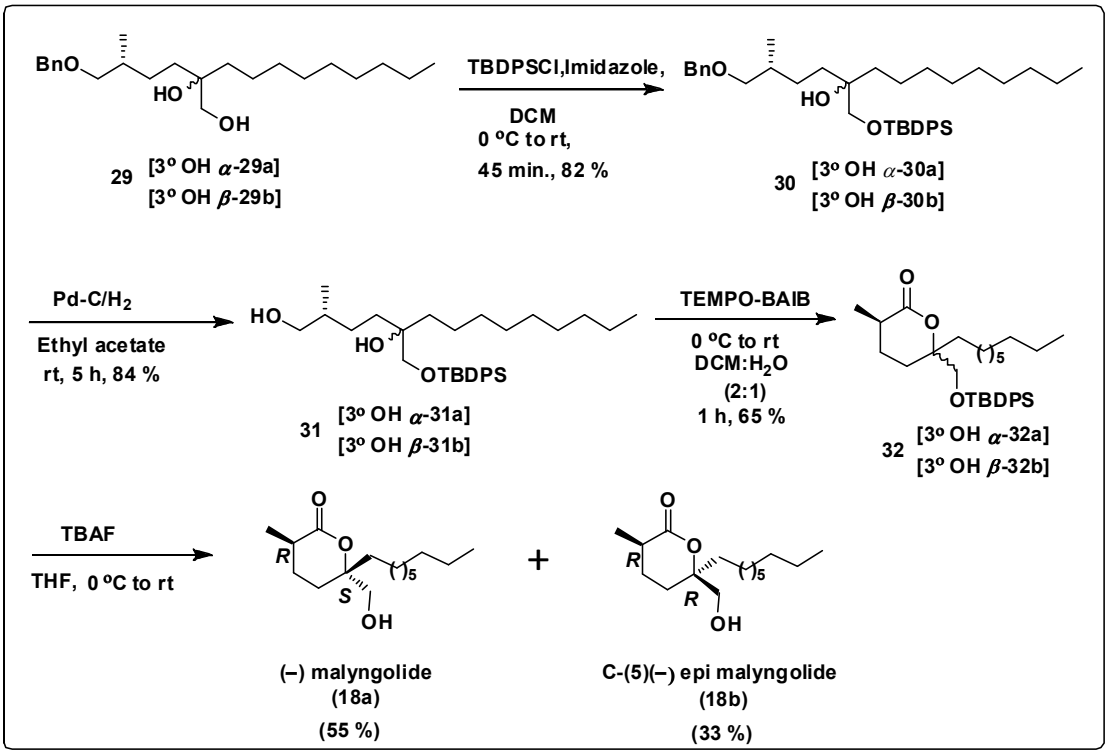
Asymmetric dihydroxylation treatment *via. in situ* formed AD-mix-α mixture through chiral ligand $(DHQ)_2PHAL$ (5 mol%), $K_3[Fe(CN)_6]$ K_2CO_3, $CH_3SO_2NH_2$ and OsO_4 (0.5 mol %), over terminal olefin **28** led to dihydroxylated product **29** with 80% yield in a mixture of diols (**29a/29b** in 6:4 diasteomeric ratio, which was confirmed in ^{1}H-NMR spectrum) (Scheme 8).

For this dihydroxylation step, various chiral ligand mediated *in situ* formed AD-mix-α mixtures were screened for e.g. $(DHQ)_2PHAL$, $(DHQ)_2AQN$, $(DHQ)_2PYR$, but slight enhancement over diastereomeric selection *i.e.* (6:4) ratio was achieved only in case of $(DHQ)_2PHAL$ ligand (in ^{1}H-NMR spectrum). Screening of this dihydroxylation reaction is summarized in **table 1**).

Table1 Screening of chiral ligand mediated Dihydroxylation step

Entry	Ligand type and mol %	Dihydroxy source	Solvent	Time (h)	Diastereomeric Ratio(%) (29a:29b)
1	Commercial AD-mix-α	K_2OsO_4	$^tBuOH:H_2O(1:1)$	10	52:48
2	$(DHQ)_2AQN$ (5)	OsO_4	$^tBuOH:H_2O(1:1)$	12	50:50
3	**$(DHQ)_2PHAL(5)$**	**OsO_4**	**$^tBuOH:H_2O(1:1)$**	**12**	**60:40**
4	$(DHQ)_2PYR(5)$	OsO_4	$^tBuOH:H_2O(1:1)$	10	51:49

Protection of diols **29a/29b** using TBDPSCl gave the mixture of mono-silyl ethers **30a/30b** in 82% yield. Subsequent debenzylation of mixture under Pd/C(10%) and H_2 atmosphere afforded again diol mixture **31a/31b** in 84% of overall yield. Latter during oxidative lactonization of diols **31a/31b** using TEMPO/BAIB gave the mixture



Scheme 9

of *δ*-lactones **32a/32b** with 65% yield. Finally, deprotection of TBDPS group from the *δ*-lactones **32a/32b** furnished the target molecules *i.e.* (—)-malyngolide **(18a**) in 55% and its C(5)(—)-epimer **(18b)** in 33% yield, which were successfully separated by column chromatography. The spectroscopic data for both stereoisomers were identical with the reported literature (Scheme 9). This linear synthetic sequence was achieved in an overall yield of 1.30% for (—)-malyngolide and 0.80% for its C(5) epimer.